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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/081,456 | 02/21/2002 | James C. Paulson | 019957-011213US | 5830 |

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| EXAMINER | |
|---|---|
| RAO, MANJUNATH N | |
| **ART UNIT** | **PAPER NUMBER** |
| 1652 | |

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/081,456 | PAULSON ET AL. | |
| | Examiner | Art Unit | |
| | Manjunath N. Rao, Ph.D. | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,21,22,59 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,21,22,59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



S102

## DETAILED ACTION

Claims 1-4, 21-22, 59, 61 are currently pending and at issue in this application.

Applicants' amendments and arguments filed on 3-14-05, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically, Examiner has withdrawn the previously held rejections under 35 U.S.C. 112, 1st and 2nd paragraphs in view claim amendments and claim cancellations. The filing of the Sequence Listing and updated first line of the specification is acknowledged.

### *Claim Rejections - 35 USC ∋ 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 21, 59, 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams et al. (Glycoconjugate J., 1995, Vol 12:755-761). This rejection is based upon the public availability of a printed publication. Claims 1-2, 5, 21, 59, 61 of the instant application are drawn to a method of sialylating a saccharide group comprising a galactose or a N-acetylgalactosamine acceptor moiety or a recombinant glycoprotein with a sialic acid donor moiety and a recombinant ST3Gal I sialyltransferase in a reaction mixture required for sialyltransferase activity for a sufficient time and conditions for transfer of sialic acid from said

sialic acid donor moiety to said saccharide moiety, wherein the sialic acid donor moiety is CMP-sialic acid, wherein a greater percentage (at least 80-90%) of the terminal saccharide residues are sialylated. Williams et al. disclose an identical method of sialylation of a glycoprotein using recombinant ST3Gal I sialyltransferase enzymes, wherein the sialic acid moiety is CMP-NANA and wherein the terminal saccharide get sialylated (see the entire document especially see page 757 columns 1 and 2). The reference does not quantitate the percent sialylation as claimed herein. However, since the reference uses saturating concentration of the substrates and an enzyme concentration of 0.15-0.4 mU of the enzyme, it can be safely concluded that the per cent sialylation falls in the range of at least 80-90%. Thus Williams et al. anticipate claims 1-2, 21, 59, 61 of this application as written.

Since the Office does not have the facilities for examining and comparing applicants' protein produced from the claimed method with the protein produced by the method claimed the prior art, the burden is on the applicant to show a novel or unobvious difference between the product formed from the claimed method and the product formed from the method of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

In response to the previous Office action, applicants have traversed the above rejection arguing that the reference does not teach the claimed method. Applicants argue that the Examiner's interpretation of the reference is incorrect. As evidence applicants submit a copy of the signed Declaration by Dr. Paulson which was previously submitted in the parent application. In the Declaration Dr. Paulson essentially maintains that the claimed method and the reference

method is not identical. Examiner respectfully disagrees and maintains that the Declaration of Dr. Paulson fails to provide such an evidence and moreover is based on limitations not recited in the claims all together. Such a disconnect from the claim limitations can be seen in the second paragraph of the declaration where Dr. Paulson declares that the "*The presently claimed features methods for sialylating a saccharide group on a recombinant glycoprotein that provide higher sialylation rates using lower sialyltransferase concentrations than are taught or suggested by the prior art*". Nowhere in the claims such a limitation is recited. Claims are not limited to any quantity of the enzyme to be used in the method. On similar lines, in the third paragraph, Dr. Paulson makes a statement that Williams et al. do not teach or suggest a sialyltransferase concentration of less than 50mU per mg of glycoprotein. Again claims are not at all limited to such specific enzyme concentrations. Furthermore, Dr. Paulson states that the Williams et al. reference only disclose some recombinant sialyltransferase. While that may be so, the claims are simply drawn to a method involving a single sialyltransferase. In the third paragraph of the declaration, Dr. Paulson goes on to state that Williams et al. reference is designed to determine the $K_M$ values of sialyltransferases and in performing such experiments, "it is necessary to maintain less than 20% saturation of substrate". However, the reference clearly indicates five different levels of substrate concentration and saturating concentrations of the acceptor molecule. Dr. Paulson goes on to make the same mistake of referring to the specific enzyme concentration in the fourth paragraph of the declaration stating that none of the references including "the secondary references teach or suggest a sialyltransferase concentration of less than about 50 mU per mg of glycopeptide". All in all the Declaration appears to be flawed and does not apply to the instant claims. In view of the above Examiner continues to

maintain his position that the reference of William s et al. anticipates claims 1-2, 21, 59, 61 as written.

***Claim Rejections - 35 USC э 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 21-22, 59, 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. (as in the above rejection) or Weinstein et al. (JBC, Vol. 237(22):13845-13850, cited in the IDS) and further in view of Wong et al. (US 5,374,541 dated 12-20-1994) and Kurosawa et al. (Biochim Biophys Acta, 1995, Vol. 1244(1):216-222) and Paulson et al. (US 5,541,083, dated 7-30-96). Claims 1-4, 21-22, 59, 61 in this instant application are drawn to a method of sialylating a saccharide group comprising a galactose or a N-acetylgalactosamine acceptor moiety or a recombinant glycoprotein with a sialic acid donor moiety and a recombinant sialyltransferase (ST) such as ST3Gal I, in a reaction mixture required for ST activity for a sufficient time and conditions for transfer of sialic acid from said sialic acid donor moiety to said saccharide moiety, wherein the sialic acid donor moiety is CMP-sialic acid, wherein the sialic acid is NeuAc is regenerated *in situ* , wherein the recombinant ST is a eukaryotic ST substantially lacking a membrane-spanning domain and comprising a sialyl motif which has an

amino acid sequence that is at least about 40% identical to sialyl motif of a natural ST, produced by a recombinant expression of a cDNA clone in a host cell such as a fungus *A.niger*.

Weinstein et al. teach a similar method of sialylating a saccharide group on a recombinant glycoprotein using ST3GalI enzyme such that 75%-100% of the acceptor sites on the glycoprotein are sialylated (see page 13846, column 2). However, the only difference between the reference method and that claimed here is that the reference method uses a purified enzyme as opposed to recombinant enzyme and still achieves 75-100% sialylation on the glycoprotein.

Williams et al. teach an *in vitro* method of sialylating a glycoprotein (discussed above) using a recombinant ST3GalI. However, the reference does not quantitate the amount of sialylation achieved.

Wong et al. teach a method of *in situ* regeneration of CMP-sialic acid for a one pot synthesis of oligosaccharides. They demonstrate the *in situ* regeneration of CMP-sialic acid such as NeuAc that sialylates formed galactosyl glycoside in the presence of a ST.

Kurosawa et al. teach or provide a recombinant clone for ST3Gal I enzyme which can be used in the above method. Paulson et al. teach a recombinant method for production of ST which lack both a membrane-spanning domain and a retention signal in order to increase the secretion of the recombinant enzymes using several types of host cells including fungi such as *A.niger* which can be used for making recombinant enzyme as provided by Kurosawa et al.

Combining the teachings of all the above references it would have been obvious to one skilled in the art at the time the invention was made to develop a large-scale or commercial scale method of sialylation of a glycoprotein under conditions using large amounts of recombinant ST

enzymes. Using the clone provided by Kurosawa et al. and the recombinant technique provide by Paulson et al. it would have been obvious for one skilled in the art to make large amounts of recombinant ST enzyme lacking membrane-spanning domain so that the recombinant enzyme would be liberated out of the cell in any eukaryotic host cell such as an insect cell line, a mammalian cell line, or a fungal cell including *A.niger* which is a commonly used host cell for production of several recombinant enzymes. Using such recombinant ST and the teachings of Wong et al. along with teachings of Weinstein et al. or Williams et al. it would have been obvious to one skilled in the art to develop a commercial scale method of sialylation with *in situ* regeneration of CMP-sialic acid in which high levels of sialylation is achieved. Combining the above teachings it would have been obvious for one skilled in the art to vary the concentrations of the enzymes, reaction conditions in terms of donor and acceptor concentrations and the number of enzymes in the reaction mix to get various percentages of sialylation such as 80-90% and various terminal groups.

One would be motivated to do this in order to study the mechanism of action of ST3Gal I or in order to make sialylated glycoproteins on a commercial scale. As the yield of these membrane bound enzymes are very poor during recombinant method of making, Paulson et al. teach that one skilled in the art would be motivated to produce recombinant ST without membrane-spanning domain so that large amounts of said enzymes liberated into the culture medium could be harvested easily. One skilled in the art would have a reasonable expectation of success since Weinstein et al. teach that up to 100% sialylation rates can be achieved using purified enzymes. In addition all the above references teach reliable and time-tested methods that has been used by a number of other inventors.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to have performed the claimed invention.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

In response to the previous Office action, applicants have traversed the above rejection. Applicants have again based their traverse on the Declaration by Dr. Paulson who has basically declared Williams et al. does not teach a method through which one can obtain 80-90% sialylation of the glycopeptide. In response to such arguments Examiner has now provided the reference of Weinstein et al. who clearly demonstrate that up to 100% sialylation of the glycoprotein can be obtained by using purified ST3Gal I enzyme.

Applicants also allege improper hindsight by the Examiner. Applicants argue that none of the reference quantitate the extent of sialylation and the reference of Williams et al. indeed teaches away from the invention because of lower specific activity. However, Examiner respectfully disagrees that applicants' arguments are persuasive because they are mainly based on a flawed Declaration by Dr. Paulson as explained above in the previous rejection. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense

necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the prior art documents that up to 100% sialylation of glycoproteins can be achieved using purified enzymes with slight contamination with other enzyme activities let alone recombinant enzymes which can be obtained in much purer form.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 21-22, 59-61 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 10 of U.S. Patent No. 6,399,336. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428,46 USPQ2d 1226 (Fed.

Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-5, 21-22, 59-61 of the instant application and claims 1-5, 10 of the reference patent are both directed to large-scale or commercial scale method of sialylating a saccharide group on a recombinant glycoprotein using , specifically a recombinant ST3Gal I. The method claimed in the instant application and the method encompassed in the reference patent are identical to one another. The portion of the specification (and the claims) in the reference patent that supports the claimed method includes several embodiments that would anticipate the method claimed in claims herein. Claims of the instant application listed above cannot be considered patentably distinct over claims 1-5, 10 of the reference patent when there is specifically recited embodiment that would anticipate mainly claims 1-5, 21-22, 59-61 of the instant application. Alternatively, claims 1-5, 21-22, 59-61 cannot be considered patentably distinct over claims 1-5, 10 of the reference patent when there is specifically disclosed embodiment in the reference patent that supports claims 1-5, 10 of that patent and falls within the scope of claims 1-5, 21-22, 59-61 herein because it would have been obvious to one having ordinary skill in the art to modify claims 1-5, 10 of the reference by selecting a specifically disclosed embodiment that supports those claims. One of ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claims 1-5, 10 of the reference patent.

In response to the above rejection, applicants maintain that they will file an appropriate terminal Disclaimer once the outstanding rejections are resolved. However, Examiner maintains the rejection for reasons of record.

***Conclusion***

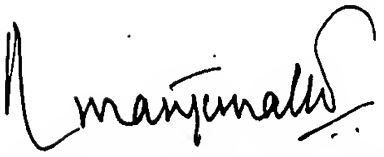
None of the claims are allowable.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306/9307 for regular communications and for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

June 2, 2005